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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/642,236	08/17/00	SCHWARTZ	G	41145-1001

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STEPHEN A SLUSHER
PEACOCK MYERS & ADAMS P C
P O BOX 26927
ALBUQUERQUE NM 87125-6927

EXAMINER	
KAM, C	
ART UNIT	**PAPER NUMBER**
1653	10

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application N .	Applicant(s)	
	09/642,236	SCHWARTZ, GEORGE R.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-22 are pending.

Applicant's response filed on August 8, 2001 (Paper No. 8) and Inventor's Declaration (Paper No. 7) have been fully considered. Claims 1 and 19 have been amended.

Objection Withdrawn

2. The previous objection of disclosure regarding the continuation data of this application at page 1 and a cited reference at page 7 is withdrawn in view of applicants' corrections.

Rejection Withdrawn

Claim Rejections-Obviousness Type Double Patenting

3. The previous rejection of claims 1-22 on nonstatutory double patenting, is withdrawn in view of applicants' abandonment of application 09/499,198.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-22 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for treating neurological damage in a mammal comprising the steps of determining the extent of neurological damage in a mammal, administering theraprutically effective amounts of thrombopoietin, or thrombopoietin and

thyroid hormone, or thrombopoietin, thyroid hormone and thyrotropin, and monitoring the extent of neurologic damage in the mammal following the administration of thrombopoietin because the specification only discloses cursory conclusions (page 1, lines 6-10, 15-18, 20-23; page 7, lines 17-26; page 9, line 6-14; page 9, line 16-20) and the claims recite no end point to the treatment, without data to support the findings, which states that thrombopoietin, or thrombopoietin and thyroid hormone, or thrombopoietin, thyroid hormone and thyrotropin can be used to treat neurological damage in human or other mammals. However, there is no data regarding the administration of thrombopoietin resulting in the regeneration and repair of damaged neurons, thus producing an effective treatment of neurologic damage either *in vitro* or *in vivo* studies. Although the three examples indicate transient improvement in the objective symptoms and a delay on the symptoms of illness in the transgenic mouse model, the effects of thrombopoietin, thyroid hormone and thyrotropin are not clearly illustrated since the three examples which use one mouse for each experiment are carried out under different treating conditions such as the administration of the agent at different days with different intervals, and the amount of agent and the composition of the agent also varying during the process of the treatment, and the means used to measure the objective symptoms are not clearly stated. Therefore, it is necessary to use a means which would indicate the effect of the agent more clearly after the treatment when compared to a placebo group without the treatment, and to have more animals in each example to show the effect is genuine, not occurring only once. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such agent. Without such guidance, the experimentation left to those skilled in the art is undue because the amount of guidance

presented is minimal that leads to a requirement for further experimentation on using a defined means to measure the effect of the thrombopoietin in an animal with neurological damage.

The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the existence of working examples, the amount of direction or guidance presented, and the amount of experimentation necessary.

In response, applicants indicate the claims are directed to " method of treatment of neurologic damage" and the efficacy of the drug in animal studies was shown in transient improvement in objective symptoms and in substantially delay onset of objective symptoms of genetically-induced disease. However, the argument is not fully persuasive because while applicant has provided more detail regarding the disease model, the design of the experiment, and the reason why control group is not needed for this disease model, applicant has not provided a defined means to measure the effect of the treatment such as measuring the stride length as described in Chiu et al. (Mol. Cell Neurosci. 6, 349-362 (1995)), and the data indicating transient improvement in the objective symptoms of animals with treatment as compared to the animal without the treatment, and the delay in the onset of the objective symptoms being meaningful since only one animal is used for each experiment. The reference by Chiu et al. shows that the state of progressive disease has been measured using a defined means, the disease model is carried out in a group of mice designated G1H including 5 males and 5 females, and the changes in weight and stride length of G1H have been monitored as compares to age-matched, nontransgenic control mice (page 351, Figures 1 and 2). The reference further

indicates vacuolar changes and neuron loss in spinal cord and brainstem of G1H mice (pages 351-356).

Applicant also indicates that "the disease expression in this animal model is progressive and without spontaneous improvement unless the effective therapy is initiated", therefore no control group is needed, and further indicates that Mouse A which received no treatment prior to onset of symptoms served as a control with respect to onset of symptoms for Mouse B. This example shows a delay of 16 days on the symptoms of illness in Mouse B as compared to Mouse A. However, the specification also indicates that Mouse C has a delay of 5 days on the symptoms of illness as compared to the onset of symptoms of Mouse A. These examples indicate there is variation in the delay of onset of symptoms in individual animals, therefore it is necessary to have more animals in each experiment in order to demonstrate the delay on the onset of symptoms is genuine, not occurring only once.

Regarding the administration of thrombopoietin resulting in increased expression of PDGF, the prior art and also the inventor's Declaration have indicated administration of thrombopoietin would increase the platelet production and endogenous PDGF production, thereby causing regeneration and repair of damaged neurons.

Regarding the requirement of undue experiment, applicant indicates the experimentation in terms of dosage, dose schedule and evaluation of endpoints are well known in the arts of pharmacology and medicinal chemistry. However, the argument is not persuasive because the dosage, dose schedule and evaluation of endpoints would be different for each disease state, in order to obtain an effective treatment of the disease, effective dose and desired outcome can only be obtained by further experimentaion.

5. Claims 1 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not describe how to determine or monitor the extent of neurologic damage in a mammal before and after the administration of thrombopoietin in a mammal, and the identities of the fragment and the variant of human thrombopoietin, nor demonstrate the fragment and the variant of human thrombopoietin have the function of enhancing production of platelets. The specification has not taught the methods for monitoring the extent of neurologic damage, the identities for the fragment and variant of human thrombopoietin, and the fragment and the variant of human thrombopoietin being functional. Therefore, the one skilled in the art would not know how to use such agents. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such agent. Without such guidance, the experimentation left to those skilled in the art is undue because the amount of guidance presented is minimal that leads to a requirement for further experimentation on monitoring the extent of neurological damage and demonstrating the function of the fragment and the variant of the thrombopoietin.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-22 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite because they lack essential steps as claimed in the process of treating neurologic damage. The

omitted steps are: the method and site of administration and a step whereby the outcome and the period for the effective treatment using thrombopoietin, or thrombopoietin and thyroid hormone, or thrombopoietin, thyroid hormone and thyrotropin can be determined.

In response, the applicant has amended the claim providing for initially determining the extent of neurologic damage and monitoring the extent of neurologic damage after the administration of the agent, and also indicates site of administration is not required unless novelty depends on such step. However, the argument is not persuasive, because there is no end point or outcome stated in the claim, as stated in the applicant's Declaration at page 3, item 6, the end point of the treatment is a delay in the onset of objective symptoms in a progressive disease or an increase in neurological function following the onset of symptoms. The site and method of administration of the agent and the period for the treatment is closely related to the outcome of the treatment for effective treatment, therefore these factors need to be included.

6. Claim 19 is indefinite because of the use of the terms "a fragment" and "a variant". The terms "a fragment" and "a variant" render the claim indefinite, it is not clear in the claim what sequence the fragment or the variant of thrombopoietin has as to human thrombopoietin.
In response, the applicant has amended the claim providing for the function for the fragment or the variant of thrombopoietin, however, neither the specification nor the claim identifies the sequences for the fragment and the variant of thrombopoietin, and the specification does not demonstrate the function of the fragment and the variant of thrombopoietin (see above item 5).

7. Claim 20 is indefinite, because it is unclear what amount of thrombopoietin is administered, e.g., the claim indicates the amount ranges from 1.0 to 100 μg/kg, it also indicates the amount can be outside the range. Use of "from....to..." or "about....to about..." is suggested

Conclusion

8. No claims are allowed.

Applicant's amendment of claims 1 and 19 necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers

for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

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October 12, 2001

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600